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TITLE OF THE INVENTION (280 characters max)

INHIBITORS OF AKT ACTIVITY

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Respectfully submitted,
Signature: Wayne J. Dustman
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Date: September 29, 2003
Registration No.: 33,870

☐ Additional inventors are being named on separately numbered sheets attached hereto.

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INHIBITORS OF AKT ACTIVITY

FIELD OF THE INVENTION

This invention relates to novel 1H-imidazo[4,5-c]pyridin-2-yl compounds, the use of such compounds as inhibitors of PKB/AKT kinase activity and in the treatment of cancer and arthritis.

BACKGROUND OF THE INVENTION

The present invention relates to 1H-imidazo[4,5-c]pyridin-2-yl containing compounds that are inhibitors of the activity of one or more of the isoforms of the serine/threonine kinase, Akt (also known as PKB). The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using the instant compounds in the treatment of cancer and arthritis.

Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-x_L, inhibits apoptotic cell death induced by various stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Aams et al. *Science,* 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase -1 related proteinases, including caspase-3, caspase- 7, caspase-8 and caspase-9 etc (Thornberry et al. *Science,* 281:1312-1316 (1998)).

The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol.Cell.Biol.* 17:1595-1606 (1997); Franke et al, *Cell,* 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science,* 275:628-630 (1997); Dudek et al., *Science,* 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-I), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (PtdIns (3,4,5)-P3), which in turn binds to, and promotes the activation of, the serine/ threonine kinase Akt, which contains a pleckstrin homology (PH)-domain (Franke et al *Cell,* 81:727-736 (1995); Hemmings *Science,* 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or

dominant negative Akt/PKB mutants abolish survival-promoting activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortrnannin) blocked the activation of Akt/PKB by upstream kinases. In addition, introduction of constitutively active PI3K or Akt/PKB mutants promotes cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).

Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed in breast and prostate cancer cell lines (Nakatani et al. *J. Biol.Chem.* 274:21528-21532 (1999).

The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of PtdIns(3,4,5)-P3, is a negative regulator of the PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Nati. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN is deleted in a large percentage of human tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt (Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).

These observations demonstrate that the PI3K/Akt pathway plays important roles for regulating cell survival or apoptosis in tumorigenesis.

Three members of the Akt/PKB subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/ PKBα, Akt2/PKBβ, and Akt3/PKBγ respectively. The isoforms are homologous, particularly in regions encoding the catalytic domains. Akt/PKBs are activated by phosphorylation events occurring in response to PI3K signaling. PI3K phosphorylates membrane inositol phospholipids, generating the second messengers phosphatidyl- inositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate, which have been shown to bind to the PH domain of Akt/PKB. The current model of Akt/PKB activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the regulatory sites of Akt/PKB by the upstream kinases occurs (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

Phosphorylation of Akt1/PKBα occurs on two regulatory sites, Thr^{308} in the catalytic domain activation loop and on Ser^{473} near the carboxy terminus (D. R. Alessi *et al. EMBO J.* 15:6541-6551 (1996) and R. Meier *et al. J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2/PKBβ and Akt3/PKBγ. The upstream kinase, which phosphorylates Akt/PKB at the activation loop site has been cloned and termed 3 '-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt/PKB, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory site of Akt/PKB near the carboxy terminus has not been identified yet, but recent reports imply a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as L Y294002 and wortmannin. However, PI3K inhibition has the potential to indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on PdtIns(3,4,5)-P3, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

Alternatively, Akt activity can be inhibited by blocking the activity of the upstream kinase PDK1. No specific PDK1 inhibitors have been disclosed. Again, inhibition of PDK1 would result in inhibition of multiple protein kinases whose activities depend on PDK1, such as atypical PKC isoforms, SGK, and S6 kinases (Williams et al. *Curr. Biol.* 10:439-448 (2000).

It is an object of the instant invention to provide novel compounds that are inhibitors of Akt/PKB.

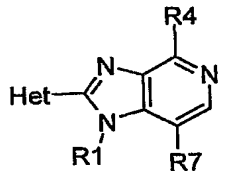
It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

It is also an object of the present invention to provide a method for treating cancer that comprises administering such inhibitors of Akt/PKB activity.

It is also an object of the present invention to provide a method for treating arthritis that comprises administering such inhibitors of Akt/PKB activity.

SUMMARY OF THE INVENTION

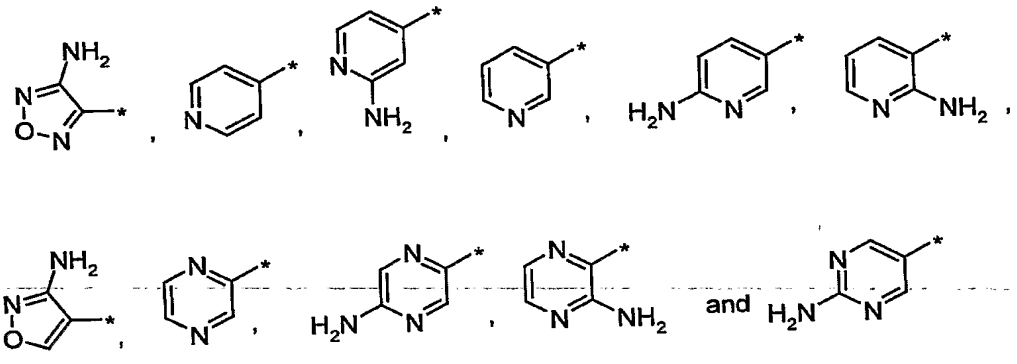
This invention relates to compounds of Formula (I):



(I)

wherein:

Het is selected from the group consisting of:



R^1 is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally

containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, $-C(O)OR^2$, $-C(O)NR^5R^6$, $-S(O)_2NR^5R^6$, $-S(O)_nR^2$ and protected -OH,
where n is 0-2,

R^2 is hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and

R^5 and R^6 are independently hydrogen, cycloalkyl, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH, or R^5 and R^6 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2; and

R^7 is selected from hydrogen, $-C(O)NR^9R^{10}$, $-(CH_2)_nNR^9R^{10}$, $-SO_2NR^9R^{10}$ and $-(CH_2)_nOR^8$,
where n is 0-2;

R^8 is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2,

R^9 and R^{10} are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, -$C(O)OR^2$, -$S(O)_nR^2$, -$C(O)NR^2R^3$, -$S(O)_2NR^2R^3$, -NR^2R^3, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH,

or R^9 and R^{10} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

This invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

This invention relates to a method of treating arthritis, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

The present invention also relates to the discovery that the compounds of Formula (I) are active as inhibitors of Akt/PKB.

In a further aspect of the invention there is provided novel processes and novel intermediates useful in preparing the presently invented Akt/PKB inhibiting compounds.

Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

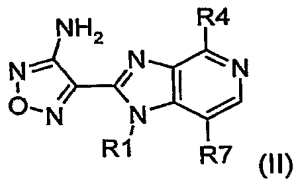
Also included in the present invention are methods of co-administering the presently invented Akt/PKB inhibiting compounds with further active ingredients.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds of Formula (I) as described above.

The presently invented compounds of Formula (I) inhibit Akt/PKB activity. In particular, the compounds disclosed selectively inhibit one, two or the three Akt/PKB isoforms.

Included among the presently invented compounds of Formula (I) are those having Formula (II):



(II)

wherein:

R^1 is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of

carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, $-C(O)OR^2$, $-C(O)NR^5R^6$, $-S(O)_2NR^5R^6$, $-S(O)_nR^2$ and protected -OH,

where n is 0-2,

R^2 is hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and

R^5 and R^6 are independently hydrogen, cycloalkyl, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH, or R^5 and R^6 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2; and

R^7 is selected from hydrogen, $-C(O)NR^9R^{10}$, $-(CH_2)_nNR^9R^{10}$, $-SO_2NR^9R^{10}$ and $-(CH_2)_nOR^8$,

where n is 0-2;

R^8 is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2,

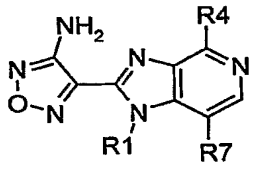
R^9 and R^{10} are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, -$C(O)OR^2$, -$S(O)_nR^2$, -$C(O)NR^2R^3$, -$S(O)_2NR^2R^3$, -NR^2R^3, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH,

or R^9 and R^{10} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (I) are those having Formula (III):



(III)

wherein:

R^1 is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more

substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, $-C(O)OR^2$, $-C(O)NR^5R^6$, $-S(O)_2NR^5R^6$, $-S(O)_nR^2$ and protected -OH,
where n is 0-2,
R^2 is hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and
R^5 and R^6 are independently hydrogen, cycloalkyl, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH, or R^5 and R^6 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,
where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2; and

R^7 is selected from $-C(O)NR^9R^{10}$, $-(CH_2)_nNR^9R^{10}$, $-SO_2NR^9R^{10}$ and $-(CH_2)_nOR^8$,
where n is 0-2;
R^8 is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one

or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR^2, -S(O)$_n$R^2, -C(O)NR^{2}R^3, -S(O)$_2$NR^{2}R^3, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2,

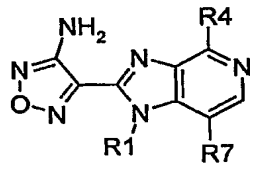
R^9 and R^{10} are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, -C(O)OR^2, -S(O)$_n$R^2, -C(O)NR^{2}R^3, -S(O)$_2$NR^{2}R^3, -NR^{2}R^3, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH,

or R^9 and R^{10} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (I) are those having Formula (IV):



(IV)

wherein:

R^1 is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy,

amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, $-C(O)OR^2$, $-C(O)NR^5R^6$, $-S(O)_2NR^5R^6$, $-S(O)_nR^2$ and protected -OH,
where n is 0-2,
R^2 is hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and
R^5 and R^6 are independently hydrogen, cycloalkyl, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH, or R^5 and R^6 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2; and

R^7 is hydrogen;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (II) are those in which:

R^1 is selected from: alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl containing from 1 to 3 heteroatoms and C_1-C_{12}aryl;

R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

R^7 is selected from hydrogen, $-C(O)NR^9R^{10}$ and $-(CH_2)_nOR^8$, where n is 0-2;

R^8 is alkyl, piperidine, imidazolidine, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, hydroxy, nitro, cyano, cycloalkyl, halogen and C_1-C_{12}aryl,

R^9 and R^{10} are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, $-NR^2R^3$, nitro, cyano, cycloalkyl, halogen, aryl and substituted aryl,

or R^9 and R^{10} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is

optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (III) are those in which:

R^1 is selected from: alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl containing from 1 to 3 heteroatoms and C_1-C_{12}aryl;

R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

R^7 is selected from $-C(O)NR^9R^{10}$ and $-(CH_2)_nOR^8$,
where n is 0-2;
R^8 is alkyl, piperidine, imidazolidine, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, hydroxy, nitro, cyano, cycloalkyl, halogen and C_1-C_{12}aryl,
R^9 and R^{10} are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, $-NR^2R^3$, nitro, cyano, cycloalkyl, halogen, aryl and substituted aryl,
or R^9 and R^{10} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is

optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (IV) are those in which:

R^1 is selected from: alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl containing from 1 to 3 heteroatoms and C_1-C_{12}aryl;

R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

R^7 is hydrogen;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the compounds useful in the present invention are:
4-(4-Phenyl-1-piperidin-4-yl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine;
4-[4-(3-Chloro-phenyl)-1-piperidin-4-yl-1H-imidazo-[4,5-c]pyridin-2-yl]furazan-3-ylamine;
4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine;
4-[1-(cyclopropylmethyl)-4-(2-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[4-(2-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

4-[1-(3-Amino-2,2-dimethylpropyl)-4-phenyl-1H-imidazo[4,5-c]pyridinyl-2-yl]-furazan-3-ylamine;
4-[4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[4-chloro-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[1-(cyclopropylmethyl)-4-(3-furanyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[1-(5-aminopentyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[1-(6-aminohexyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[1-(5-aminopentyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[1-(6-aminohexyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-methoxyphenyl)-1H-imidazo[4,5-c]pyridinyl-2-yl]-furazan-3-ylamine;
4-[1-(5-aminopentyl)-4-(3-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[1-(6-aminohexyl)-4-(3-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

4-[4-phenyl-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[4-(3-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[4-(4-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[1-(3-aminopropyl)-4-(2-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[1-(3-aminopropyl)-4-(1-piperidinyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-phenyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;
1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-thiophen-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;
1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;
1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;
1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-furan-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;
1-[2-(4-Amino-furazan-3-yl)-4-chloro-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
1-[2-(4-Amino-furazan-3-yl)-4-(1H-pyrrol-2-yl))-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-methoxyphenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-furan-2-yl-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
2-(4-Amino-furazan-3-yl)-1-ethyl-4-phenyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;
2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;
2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2,3-dichloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;
2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;
2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-hydroxy-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;
2-(4-Amino-furazan-3-yl)-4-(3-chloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
2-(4-Amino-furazan-3-yl)-4-phenyl-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
2-(4-Amino-furazan-3-yl)-4-(5-chloro-thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

2-(4-Amino-furazan-3-yl)-4-(2-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
2-(4-Amino-furazan-3-yl)-4-(3-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
2-(4-Amino-furazan-3-yl)-4-(3-bromo-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
2-(4-Amino-furazan-3-yl)-4-(1-naphthalenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
2-(4-Amino-furazan-3-yl)-4-(thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
2-(4-Amino-furazan-3-yl)-4-(3,4-methylenedioxyphenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
2-(4-Amino-furazan-3-yl)-4-(3,5-dichloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-biphenylyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,4-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(phenylethynyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;
4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
(2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenyl)methanol;
2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}-4-chlorophenol;
4-(1-ethyl-7-{[3-(methylamino)-1-pyrrolidinyl]carbonyl}-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;
4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(4-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,5-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(1-benzothien-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[1-ethyl-4-phenyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-{7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-[4-(methyloxy)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-1,2,5-oxadiazol-3-amine;
4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;
4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
4-[4-(3-chlorophenyl)-1-ethyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-{2-[(phenylmethyl)amino]ethyl}-1H-imidazo[4,5-c]pyridine-7-carboxamide;
4-[1-Ethyl-7-(piperidin-4-yloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
3-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;
4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}benzonitrile;
1-[2-(4-Amino-furazan-3-yl)-4-phenyl-1-piperidin-4yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
4-(4-(3-chlorophenyl)-1-ethyl-7-{[3-(methylamino)-1-pyrrolidinyl]carbonyl}-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;
4-(4-(2,5-dichlorophenyl)-1-ethyl-7-{[3-(methylamino)-1-pyrrolidinyl]carbonyl}-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;
4-[4-(2,5-dichlorophenyl)-1-ethyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine; and
2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-[3-(dimethylamino)propyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide;
and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention.

By the term "protected hydroxy" or "protected -OH" as used herein, is meant the alcoholic or carboxylic-OH groups which can be protected by conventional blocking groups in the art such as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York.

Compounds containing protected hydroxy groups may also be useful as intermediates in the preparation of the pharmaceutically active compounds of the invention.

By the term "aryl" as used herein, unless otherwise defined, is meant a cyclic or polycyclic aromatic ring containing from 1 to 14 carbon atoms and optionally containing from one to five heteroatoms, provided that when the number of carbon atoms is 1 the aromatic ring contains at least four heteroatoms, when the number of carbon atoms is 2 the aromatic ring contains at least three heteroatoms, when the number of carbons is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom.

By the term "C_1-C_{12}aryl" as used herein, unless otherwise defined, is meant phenyl, naphthalene, 3,4-methylenedioxyphenyl, pyridine, biphenyl, quinoline, pyrimidine, quinazoline, thiophene, furan, pyrrole, pyrazole, imidazole benzothiohpene and tetrazole.

The term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has one or more substituents selected from the group consisting of: $-CO_2R^{20}$, aryl, $-C(O)NHS(O)_2R^{20}$, $-NHS(O)_2R^{20}$, hydroxyalkyl, alkoxy, $-C(O)NR^{21}R^{22}$, acyloxy, alkyl, amino, methylamino, dimethylamino, N-acylamino, hydroxy, $-(CH_2)_gC(O)OR^{23}$, $-S(O)_nR^{23}$, nitro, tetrazole, cyano, oxo, halogen, trifluoromethyl and protected -OH, where g is 0-6, R^{23} is hydrogen or alkyl, R^{20} is selected form hydrogen, C_1-C_4alkyl, aryl and trifluoromethyl, and R^{21} and R^{22} are independently selected form hydrogen, C_1-C_4alkyl, aryl and trifluoromethyl, and n is 0-2.

By the term "alkoxy" as used herein is meant -Oalkyl where alkyl is as described herein including $-OCH_3$ and $-OC(CH_3)_2CH_3$.

The term "cycloalkyl" as used herein unless otherwise defined, is meant a nonaromatic, unsaturated or saturated, cyclic or polycyclic C_3-C_{12}.

Examples of cycloalkyl and substituted cycloalkyl substituents as used herein include: cyclohexyl, 4-hydroxy-cyclohexyl, 2-ethylcyclohexyl, propyl 4-methoxycyclohexyl, 4-methoxycyclohexyl, 4-carboxycyclohexyl, cyclopropyl and cyclopentyl.

By the term "acyloxy" as used herein is meant -OC(O)alkyl where alkyl is as described herein. Examples of acyloxy substituents as used herein include: $-OC(O)CH_3$, $-OC(O)CH(CH_3)_2$ and $-OC(O)(CH_2)_3CH_3$.

By the term "N-acylamino" as used herein is meant -N(H)C(O)alkyl, where alkyl is as described herein. Examples of N-acylamino substituents as used herein include: $-N(H)C(O)CH_3$, $-N(H)C(O)CH(CH_3)_2$ and $-N(H)C(O)(CH_2)_3CH_3$.

By the term "aryloxy" as used herein is meant -Oaryl where aryl is phenyl, naphthyl, 3,4-methylenedioxyphenyl, pyridyl or biphenyl optionally substituted with one or more substituents selected from the group consisting of: alkyl, hydroxyalkyl, alkoxy, trifuloromethyl, acyloxy, amino, N-acylamino, hydroxy, $-(CH_2)_gC(O)OR^{25}$, $-S(O)_nR^{25}$, nitro, cyano, halogen and protected -OH, where g is 0-6, R^{25} is hydrogen or alkyl, and n is 0-2. Examples of aryloxy substituents as used herein include: phenoxy, 4-fluorophenyloxy and biphenyloxy.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or sulfur.

By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

By the term "alkyl" and derivatives thereof and in all carbon chains as used herein is meant a linear or branched, saturated or unsaturated hydrocarbon chain, and unless otherwise defined, the carbon chain will contain from 1 to 12 carbon atoms. Examples of alkyl substituents as used herein include: $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-(CH_2)_3-CH_3$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH_2-CH_3$, $-CH=CH_2$, and $-C\equiv C-CH_3$.

By the term "treating" and derivatives thereof as used herein, is meant prophylatic and therapeutic therapy.

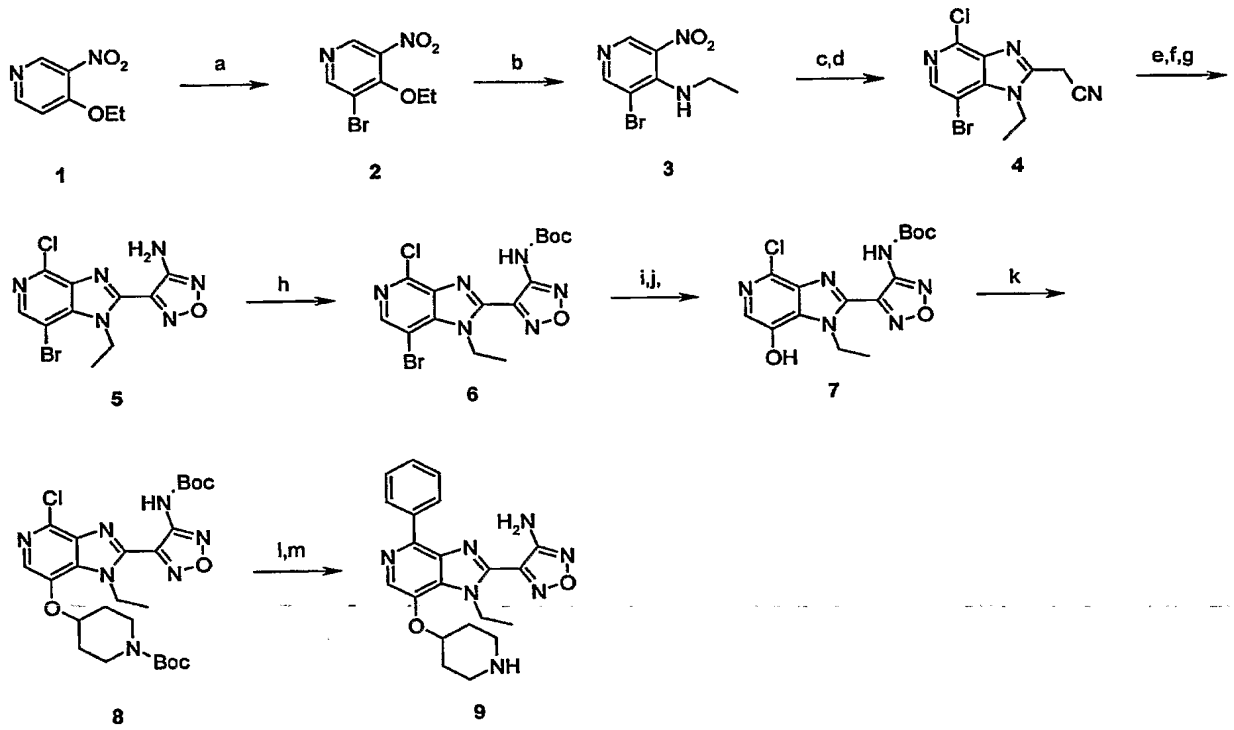
All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention. Where a -COOH or -OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, pivaloyloxymethyl, and the like for -COOH, and acetate maleate and the like for -OH, and those esters known in the art for modifying solubility or hydrolysis characteristics, for use as sustained release or prodrug formulations.

The novel compounds of Formulas I, II, III and IV are prepared as shown in Schemes I to III below, or by analogous methods, wherein the 'Het' and 'R' substituents are as defined in Formulas I, II, III and IV respectively and provided that the 'Het' and 'R' substituents do not include any such substituents that render inoperative the processes of Schemes I to IV. All of the starting materials are

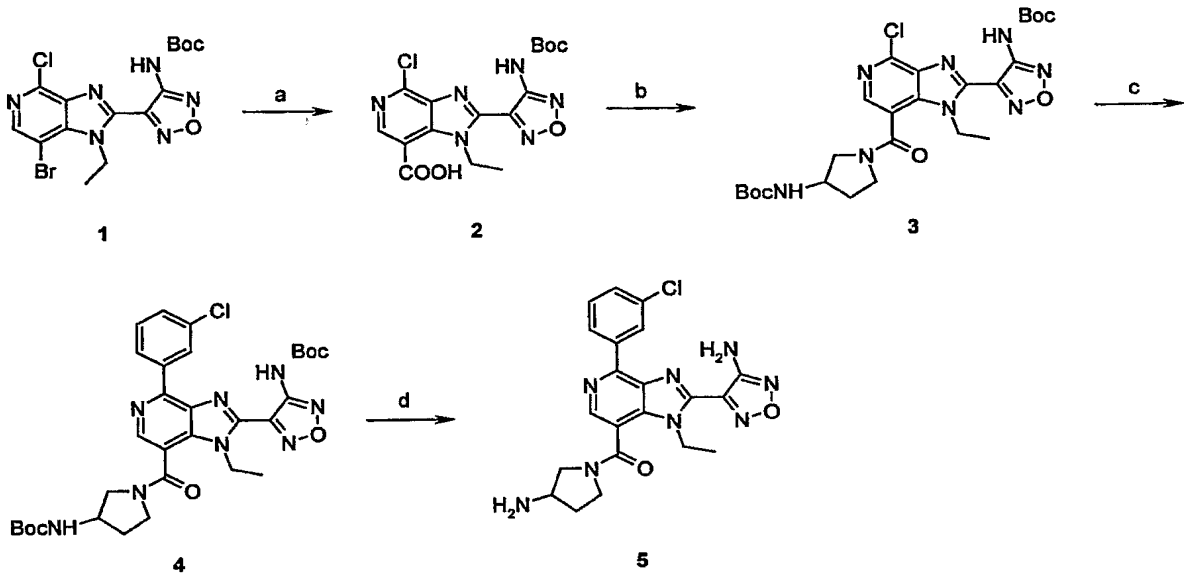
commercially available or are readily made from commercially available starting materials by those of skill in the art.

SCHEME 1



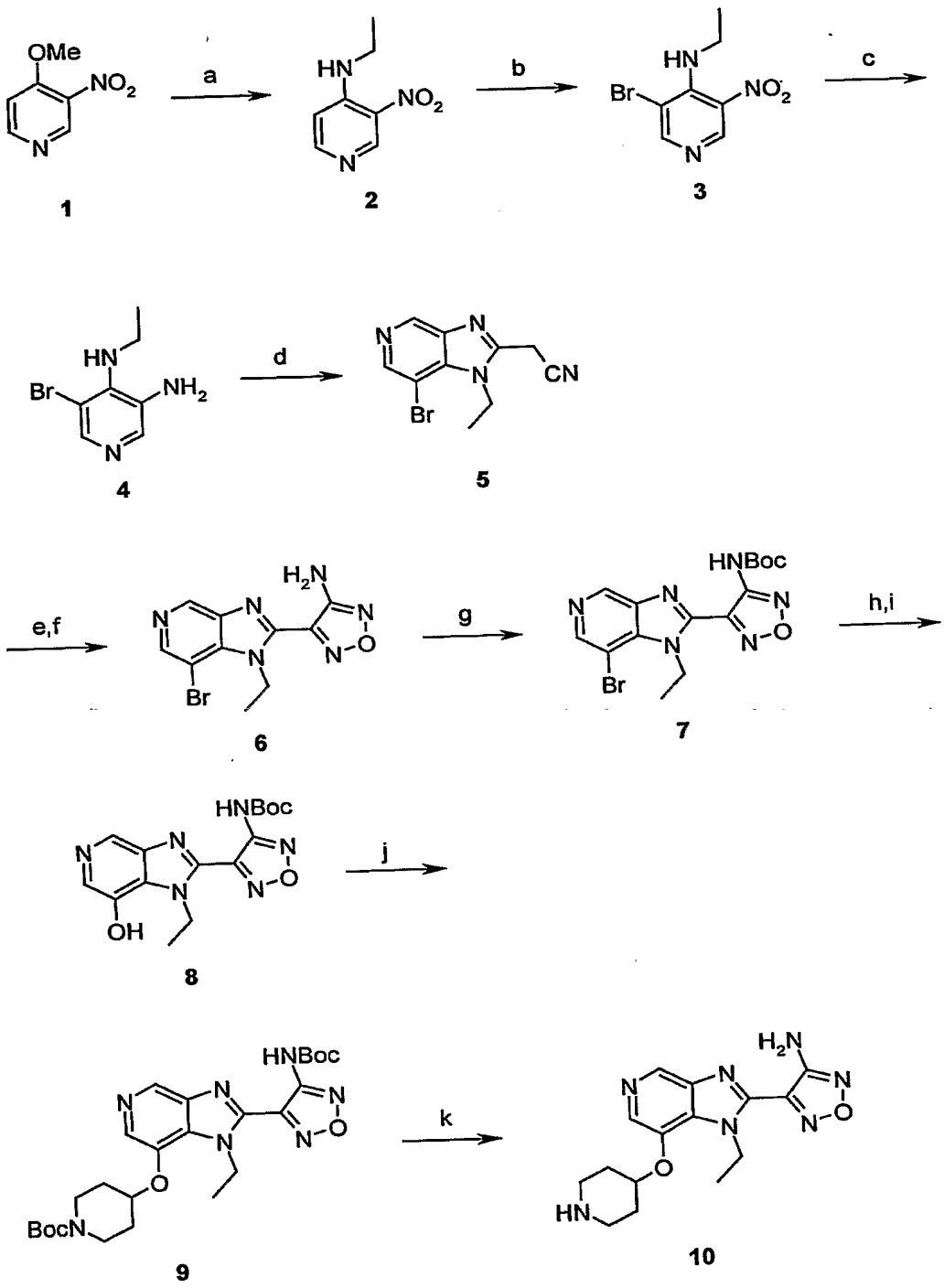
(a) Br_2, NaOAc, AcOH, 60 °C; (b) $EtNH_2$; (c) $SnCl_2$, HCl; (d) ethyl cyanoacetate, 190 °C; (e) $NaNO_2$, HCl; (f) NH_2OH; (g) Et_3N, dioxane, 150 °C; (h) di-t-butyldicarbonate, DMAP, pyridine; (i) i - n-BuLi, -78 °C. ii - $B(OMe)_3$; (j) H_2O_2, NaOH; (k) 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate, polymer-bound Ph_3P, DEAD, CH_2Cl_2/THF; (l) $PhB(OH)_2$, $(Ph_3P)_4Pd$, 2M Na_2CO_3, toluene/EtOH; (m) TFA, CH_2Cl_2.

SCHEME 2



(a) i - n-BuLi, ii - CO_2; (b) 1,1-dimethylethyl 3-pyrrolidinylcarbamate, EDCI, HOAt, NMM; (c) (3-chlorophenyl)$B(OH)_2$, $(Ph_3P)_4Pd$, 2M Na_2CO_3, toluene; (d) TFA.

SCHEME 3



(a) $EtNH_2$; (b) Br_2, NaOAc, AcOH; (c) Fe powder, AcOH; (d) ethyl cyanoacetate, 190 °C; (e) $NaNO_2$; (f) NH_2OH; (g) di-t-butyldicarbonate, DMAP, pyridine; (h) i -

n-BuLi, ii - $B(OMe)_3$; (i) H_2O_2, NaOH; (j) 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate, polymer-bound Ph_3P, DEAD, CH_2Cl_2; (k) TFA.

By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of an AKT inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment, or to be useful in the treatment of arthritis. The term further active ingredient or ingredients, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer or arthritis. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Examples of a further active ingredient or ingredients for use in combination with the presently invented Akt inhibiting compounds are chemotherapeutic agents.

Because the pharmaceutically active compounds of the present invention are active as Akt inhibitors they exhibit therapeutic utility in treating cancer and arthritis.

Isolation and Purification of His-tagged AKT1 (aa 136-480)

Insect cells expressing His-tagged AKT1 (aa 136-480) were lysed in 25 mM HEPES, 100 mM NaCl, 20 mM imidazole; pH 7.5 using a polytron (5 mLs lysis buffer/g cells). Cell debris was removed by centrifuging at 28,000 x *g* for 30 minutes. The supernatant was filtered through a 4.5-micron filter then loaded onto a nickel-chelating column pre-equilibrated with lysis buffer. The column was washed with 5 column volumes (CV) of lysis buffer then with 5 CV of 20% buffer B, where buffer B is 25 mM HEPES, 100 mM NaCl, 300 mM imidazole; pH 7.5. His-tagged AKT1 (aa 136-480) was eluted with a 20-100% linear gradient of buffer B over 10 CV. His-tagged AKT1 (136-480) eluting fractions were pooled and diluted 3-fold with buffer C, where buffer C is 25 mM HEPES, pH 7.5. The sample was then chromatographed over a Q-Sepharose HP column pre-equilibrated with buffer C. The column was washed with 5 CV of buffer C then step eluted with 5 CV

10%D, 5 CV 20% D, 5 CV 30% D, 5 CV 50% D and 5 CV of 100% D; where buffer D is 25 mM HEPES, 1000 mM NaCl; pH 7.5. His-tagged AKT1 (aa 136-480) containing fractions were pooled and concentrated in a 10-kDa molecular weight cutoff concentrator. His-tagged AKT1 (aa 136-480) was chromatographed over a Superdex 75 gel filtration column pre-equilibrated with 25 mM HEPES, 200 mM NaCl, 1 mM DTT; pH 7.5. His-tagged AKT1 (aa 136-480) fractions were examined using SDS-PAGE and mass spec. The protein was pooled, concentrated and frozen at –80C.

His-tagged AKT2 (aa 138-481) and His-tagged AKT3 (aa 135-479) were isolated and purified in a similar fashion.

Compounds of the invention are tested for potency as Akt inhibitors by known methods, such as described in International Application No. PCT/US02/10880.

The pharmaceutically active compounds within the scope of this invention are useful as Akt inhibitors in mammals, particularly humans, in need thereof.

The present invention therefore provides a method of treating cancer, arthritis and other conditions requiring Akt inhibition, which comprises administering an effective compound of Formula (I) or a pharmaceutically acceptable salt, hydrate, solvate or ester thereof. The compounds of Formula (I) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as Akt inhibitors. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid;. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft

gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of an Akt inhibitor, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular Akt inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing Akt inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an effective Akt inhibiting amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use as an Akt inhibitor.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in therapy.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating cancer.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating arthritis.

The invention also provides for a pharmaceutical composition for use as an Akt inhibitor which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in treating arthritis which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer or arthritis, or compounds known to have utility when used in combination with an Akt inhibitor.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

Experimental Details

The compounds of Examples 1 to 72 are readily made according to Schemes I to III or by analogous methods.

Example 1

Preparation of 4-(4-Phenyl-1-piperidin-4-yl-1*H*-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine

a) (1-Benzyl-piperidin-4-yl)-(3-nitro-pyridin-4-yl)-amine

A mixture of 4-methoxy-3-nitropyridine (4.34 g, 28.1 mmol), 4-amino-1-benzypiperidine (6.01 g, 30.9 mmol), and Na_2OAc (2.31 g, 28.1 mmol) in absolute ethanol (20 mL) was stirred at reflux for 54 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with water (2 x 30 mL). The organic layer was dried

over anhydrous $MgSO_4$ and concentrated *in vacuo* to provide the product (8.78 g) as a dark yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1 H), 8.26 (dd, J = 6.0, 0.4 Hz, 1 H), 8.20 (broad d, J = 7.1 Hz, 1 H), 7.34-7.25 (complex m, 5 H), 6.70 (d, J = 6.0 Hz, 1 H), 3.62-3.53 (m, 1 H), 3.55 (s, 2 H), 2.89-2.79 (m, 2 H), 2.30-2.20 (m, 2 H), 2.10-2.00 (m, 2 H), 1.76-1.65 (m, 2 H).

b) N^4-(1-Benzyl-piperidin-4-yl)-2-chloro-pyridin-3,4-diamine

To a stirred solution of the compound of Example 1(a) (3.00 g, 9.60 mmol) in conc. HCl at 90 °C was added tin (II) chloride (9.09 g, 48.0 mmol) portionwise over 10-15 min, at which time the resultant mixture was stirred at 90 °C for additional 30 min. The reaction was cooled to ambient temperature, and the precipitated product (HCl salt thereof) was collected via filtration. The free base was isolated upon treatment of the hydrochloride salt with excess 2.5 N NaOH, followed by an exhaustive extraction with CH_2Cl_2, drying of the combined organic extracts over anhydrous $MgSO_4$, and solvent evaporation. Additional product can be obtained upon treatment of the HCl filtrate with 50% NaOH solution, followed by removal of the tin salts via filtration, and extraction of the filtrate with CH_2Cl_2. A total of 3.00 g of the product was obtained as a yellow foamy solid. MS (ES+) m/z 317.2 $[M+H]^+$.

c) [1-(1-Benzyl-piperidin-4-yl)-4-chloro-1*H*-imidazo[4,5-c]pyridin-2-yl]-acetonitrile

A mixture of the compound of Example 1(b) (2.10 g, 6.63 mmol) and ethyl cyanoacetate (5 mL, 46.4 mmol) was heated at 190 °C for 2.5 h. Purification of the crude reaction mixture by flash chromatography (silica gel, 50:1→35:1→20:1 CH_2Cl_2/MeOH gradient) provided the product (1.44 g) as a deep yellow foamy solid. MS (ES+) m/z 366.2 $[M+H]^+$.

d) [1-(1-Benzyl-piperidin-4-yl)-4-phenyl-1*H*-imidazo[4,5-c]pyridin-2-yl]-acetonitrile

A solution of the compound of Example 1(c) (185 mg, 0.506 mmol), phenylboronic acid (92 mg, 0.758 mmol), and $Pd(PPh_3)Cl_2$ (35 mg, 0.0506 mmol) in toluene (5 mL) at ambient temperature was treated with a 2 *M* solution of sodium carbonate, and the resultant dark biphasic mixture was heated at reflux for 3 h. The reaction was cooled to ambient temperature, concentrated *in vacuo*, and purified by flash chromatogrphy (silica gel, 30:1→10:1 CH_2Cl_2/MeOH gradient) to give the product (177 mg) as a yellow crystalline solid. MS (ES+) m/z 408.2 $[M+H]^+$.

e) [1-(1-Benzyl-piperidin-4-yl)-4-phenyl-1*H*-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

To a solution of the compound of Example 1(d) (165 mg, 0.405 mmol) in MeOH (4 mL) and 2 *N* HCl (1.5 mL, 3.00 mmol) was added sodium nitrite (56 mg, 0.810 mmol) portionwise. The reaction mixture was stirred at ambient temperature for 1.5 h, at which time the pH of the solution was adjusted to 12 with 50 wt. % NaOH aqueous solution. The resultant dark mixture was then treated with hydroxylamine (50 wt. % solution in water, 1.1 mL, 17.95 mmol) and stirred at 90 °C for 15 h. After allowing the reaction to cool to RT, the resulting yellow precipitate was isolated by filtration, washed with cold MeOH and dried under high vacuum to give pure product (85 mg). MS (ES+) m/z 452.2 $[M+H]^+$.

f) 4-(4-Phenyl-1-piperidin-4-yl-1*H*-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine

A solution of the compound of Example 1(e) (33 mg, 0.073 mmol) in dry CH_2Cl_2 (2.5 mL) at RT was treated with 1-chloroethyl chloroformate (24 μL, 0.219 mmol). The resultant mixture was heated at reflux for 1 h, then cooled to RT and concentrated *in vacuo*. The residue was then heated at reflux in MeOH for 1 h. The product was isolated by preparative HPLC (Zorbax C18 column, 7 micron particle size, 250 mm x 21.2 mm i.d.; 20-90% acetonitrile/water (0.1 % TFA); 20 mL/min; UV detection at 254 nm; R_t = 4.3 min) to afford the product (27 mg) as a white solid. MS (ES+) m/z 362.2 $[M+H]^+$.

Example 2

Preparation of 4-[4-(3-Chloro-phenyl)-1-piperidin-4-yl-1*H*-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

a) [1-(1-Benzyl-piperidin-4-yl)-4-(3-chloro-phenyl)-1*H*-imidazo[4,5-c]pyridin-2-yl]-acetonitrile

The compound was prepared in a manner analogous to the preparation of the compound of Example 1(d), except substituting 3-chlorophenylboronic acid for phenylboronic acid. MS (ES+) m/z 442.4 $[M+H]^+$.

b) [1-(1-Benzyl-piperidin-4-yl)-4-(3-chloro-phenyl)-1*H*-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

The compound was prepared in a manner analogous to the preparation of the compound of Example 1(e), except substituting the compound of Example 2(a) for the compound of Example 1(e). MS (ES+) m/z 486.4 $[M+H]^+$.

c) 4-[4-(3-Chloro-phenyl)-1-piperidin-4-yl-1*H*-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

The title compound was prepared in a manner analogous to the preparation of the compound of Example 1(f), except substituting the compound of Example 2(b) for the compound of Example 1(e). MS (ES+) m/z 396.0 $[M+H]^+$.

Example 3

Preparation of 4-[1-(3-amino-2,2-dimethylpropyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

a) N^1-(3-Nitropyridin-4-yl)-2,2-dimethyl-1,3-propanediamine

A solution of 4-methoxy-3-nitropyridine (5.00 g, 32.4 mmol) and 2,2-dimethyl-1,3-propanediamine (16.2 g, 161 mmol) in DMF (100 mL) was heated at 100 °C for 5 h. The solvent was removed under reduced pressure to give 7.30 g of the desired compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 2H), 9.10 (br, 1H), 8.20 (d, 1H), 6.70 (d, 1H), 3.25 (d, 2H), 2.60 (s, 2H), 1.25 (br, 2H), 0.95 (s, 6H).

b) 2-[3-(3-Nitropyridin-4-ylamino)-2,2-dimethylpropyl]-isoindole-1,3-dione

A solution of the compound of Example 3(a) (7.30 g, 32.4 mmol) and phthalic anhydride (4.80 g, 32.4 mmol) in glacial acetic acid (160 mL) was heated overnight at 120 °C. After 16 h, the solution was allowed to cool to RT and the solvent was removed *in vacuo*. The residue was partitioned between EtOAc (650 mL) and 5% $NaHCO_3$ (100 mL). The organic layer was washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to give 10.5 g of the desired compound. MS (ES) m/z 355.2 $[M+H]^+$.

c) 2-[3-(3-Amino-2-chloropyridin-4-ylamino)-2,2-dimethylpropyl]-isoindole-1,3-dione

A suspension of the compound of Example 3(b) (10.5 g, 29.6 mmol) in conc. HCl (220 mL) was heated to 70 °C and tin (II) chloride dihydrate (35.3 g, 157 mmol) added portionwise. The solution was heated for 30 min at 90 °C, allowed to cool and then filtered. The collected solid was partitioned between EtOAc (750 mL) and 0.5N NaOH (200 mL). This mixture was filtered and the filter cake slurried with

1.0N NaOH (75 mL). The slurry was extracted with EtOAc (2 x 250 mL) and the combined organic layers were washed with brine (70 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give 5.41 g of the desired compound. MS (ES) m/z 359.2 $[M+H]^+$.

d) 4-Chloro-1-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2,2-dimethylpropyl]-1H-imidazo[4,5-c]pyridin-2-yl]-acetonitrile

A mixture of the compound of Example 3(c) (5.40 g, 150 mmol) and ethyl cyanoacetate (15 mL) was heated at 190 °C. After 6 h, the cooled crude reaction mixture was subjected to flash chromatography (silica gel, Et_2O to 50% Et_2O/CH_2Cl_2) to give 1.70 g of the desired compound. MS (ES) m/z 408.0 $[M+H]^+$.

e) 4-Chloro-1-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2,2-dimethylpropyl]-1H-imidazo[4,5-c]pyridin-2-yl]-hydroxyiminoacetonitrile

Sodium nitrite (0.15 g, 2.20 mmol) was added to a stirred suspension of the compound of Example 3(d) (0.45 g, 1.10 mmol) in a mixture of MeOH (10 mL) and 2N HCl (4.4 mL). After 18 h, the product was isolated by filtration to give 0.41 g of the desired compound. MS (ES) m/z 437.0 $[M+H]^+$.

f) 4-Chloro-1-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2,2-dimethylpropyl]-1H-imidazo[4,5-c]pyridin-2-yl]-N-hydroxy-2-hydroxyiminoacetamidine

A solution of the compound of Example 3(e) (0.40 g, 0.92 mmol), Et_3N (1.4 mL) and 50% aqueous hydroxylamine (0.25 mL) in THF (20 mL) was heated in a sealed flask at 90 °C. After 1 h, the reaction was allowed to cool to RT and was partitioned between EtOAc (125 mL) and water (50 mL). The organic layer was washed with water (50 mL), brine (40 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to give 0.42 g of the desired compound. MS (ES) m/z 470.2 $[M+H]^+$.

g) 2-{3-[2-(4-Aminofurazan-3-yl)-4-chloro-1H-imidazo[4,5-c]pyridin-1-yl]-2,2-dimethylpropyl}-isoindole-1,3-dione

A solution of the compound of Example 3(f) (0.42 g, 0.91 mmol) in a mixture of dioxane (14 mL) and Et_3N (1.4 mL) was heated to 150 °C in a sealed flask. After 1 h, the reaction was allowed to cool to RT and the solvent was removed *in vacuo*. Flash chromatography (silica gel, 3% $MeOH/CH_2Cl_2$) gave 0.32 g of the desired compound. MS (ES) m/z 452.2 $[M+H]^+$.

h) N-{3-[2-(4-Aminofurazan-3-yl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-1-yl]-2,2-dimethylpropyl}-phthalamic acid

A stirred mixture of toluene (5 mL), EtOH (5 mL), 3-chlorophenyl-boronic acid (0.045 g, 0.29 mmol) and the compound of Example 3(g) (0.10 g, 0.22 mmol) was treated with 1.0 M Na_2CO_3 (0.6 mL) followed by $(Ph_3P)_4Pd$ (0.025g, 0.022 mmol). After 5 h at reflux, the solvent was removed *in vacuo* and the residue was dissolved in water (5 mL). The solution was adjusted to pH 5 with 0.2 N HCl and the resulting suspension was extracted with EtOAc (3 x 75 mL). The combined extracts were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the by preparative HPLC (10 to 50% acetonitrile/water, 0.1% TFA over 10 min., 50 x 20 mm. I.D. YMC Combi-Prep ODS-A) gave 0.068 g of the desired compound. MS (ES) 546.2 $[M+H]^+$.

i) 4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

A solution of the compound of Example 3(h) (0.055 g, 0.083 mmol) in a mixture of EtOH (7 mL) and hydrazine hydrate (3 mL) was heated at reflux for 20 h. The solvent was removed *in vacuo* and the residue subjected to preparative HPLC (10 to 50% acetonitrile/water, 0.1% TFA over 10 min., 50 x 20 mm. I.D. YMC Combi-Prep ODS-A) to give 0.020 g of the title compound. MS (ES) m/z 398.2 $[M+H]^+$.

Example 4

Preparation of 4-[1-(cyclopropylmethyl)-4-(2-methylphenyl)-1*H*-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

In a manner analogous to the prepartion of the compound of Example 7, the compound of Example 8(e) (100 mg, 0.31 mmol) and *o*-tolyl boronic acid (47 mg, 0.52 mmol) gave the title compound (27 mg). MS(ES+) m/e 347 $[M+H]^+$.

Example 5

Preparation of 4-[4-(2-chlorophenyl)-1-(cyclopropylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

In a manner analogous to the prepartion of the compound of Example 7, the compound of Example 8(e) (100 mg, 0.31 mmol) and 2-chlorophenyl boronic acid (80 mg, 0.52 mmol) gave the title compound (20 mg). MS(ES+) m/e 367 $[M+H]^+$.

Example 6

Preparation of 4-[1-(3-amino-2,2-dimethylpropyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

a) N-{3-[2-(4-Aminofurazan-3-yl)-4-phenyl-1H-imidazo[4,5-c]pyridin-1-yl]-2,2-dimethylpropyl}-phthalamic acid

In a procedure similar to that of Example 3(h), phenylboronic acid (0.035 g, 0.29 mmol) and the compound of Example 3(g) (0.100 g, 0.22 mmol) gave the desired compound. MS (ES) m/z 512.2 $[M+H]^+$.

b) 4-[1-(3-Amino-2,2-dimethylpropyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

In a procedure similar to that of Example 3(g), the compound of Example 6(a) gave 0.030 g of the title compound. MS (ES) m/z 364.2 $[M+H]^+$.

Example 7

Preparation of 4-[4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

A mixture of toluene (8.4 mL) and 2M Na_2CO_3 (1.0 mL) was deoxygenated by purgin with nitrogen. The compound of Example 8(e) (100 mg, 0.31 mmol), 3-chlorophenyl boronic acid (81 mg, 0.52 mmol), and dichlorobis(triphenylphosphine)palladium(II) (24 mg, 0.035 mmol) were added and the mixture was heated to 100 °C for 16 h. After cooling to RT, the reaction was concentrated *in vacuo*. Flash chromatography (silica gel, MeOH/$CHCl_3$ gradient) gave the title compound (66 mg). MS(ES+) m/e 367 $[M+H]^+$.

Example 8

Preparation of 4-[4-chloro-1-(cyclopropylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

a) *N*-(Cyclopropylmethyl)-3-nitro-4-pyridinamine

4-methoxy-3-nitropyridine (10.0 g, 64 mmol), cyclopropylmethyl amine (4.56 g, 64 mmol), and EtOH (7 mL) were combined in a sealed tube and heated to 85 °C with vigourous shaking for 48 h. The mixture was concentrated *in vacuo* to afford the desired compound as a solid (12.0 g). MS(ES+) m/z 194 $[M+H]^+$.

b) 2-Chloro-N^4-(cyclopropylmethyl)-3,4-pyridinediamine

A solution of the compound of Example 8(a) (12.0 g, 62 mmol) in EtOH (136 mL) was cooled to 0 °C. Conc. HCl (136 mL) was added and the mixture was stirred at 0 °C for 15 min. Tin (II) chloride dihydrate (42.2 g, 188 mmol) was added and stirring was continued at 0 °C for 3 h. The reaction was quenched by adjusting to pH 8 with 1M NaOH. The mixture was extracted with EtOAc (200 mL x 3) and the combined extracts were washed with brine (300 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired compound (3.98 g). MS(ES+) m/z 198 $[M+H]^+$.

c) [4-Chloro-1-(cyclopropylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]acetonitrile

The compound of Example 8(b) (3.98 g, 20 mmol), ethylcyanoacetate (10 mL, 94 mmol), and *N,N*-dimethylacetamide (10 mL) were combined in a sealed tube and heated to 150 °C for 3 h. The mixture was cooled to RT and concentrated *in vacuo*. Flash chromatography (silica gel, MeOH/$CHCl_3$ gradient) yielded the desired compound (3.83 g). MS(ES+) m/z 247 $[M+H]^+$.

d) (2*E*)-[4-Chloro-1-(cyclopropylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl](hydroxyimino)ethanenitrile

Sodium nitrite (2.11 g, 31 mmol) was added to a solution of the compound of Example 8(c) (3.83 g, 16 mmol) in MeOH (110 mL) and 2M HCl (50 mL). The mixture was stirred at RT for 1.5 h and then cooled to 0 °C. The resulting precipitate was collected via filtration, rinsed with cold water and dried to afford the desired compound as a yellow solid (2.4 g). MS(ES+) m/z 276 $[M+H]^+$.

e) 4-[4-Chloro-1-(cyclopropylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

The compound of Example 8(d) (2.4 g, 8.7 mmol), THF (58 mL), Et_3N (4.7 mL), and 50% aqueous hydroxylamine (1.56 mL) were combined in a sealed tube and heated to 100 °C for 48 h. The mixture was then cooled to RT and concentrated *in vacuo*. Flash chromatography (silica gel, MeOH/$CHCl_3$ gradient) yielded the title compound (1.6 g). MS(ES+) m/z 291 $[M+H]^+$.

Example 9

Preparation of 4-[1-(cyclopropylmethyl)-4-(3-furanyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

In a manner analogous to the prepartion of the compound of Example 7, the compound of Example 8(e) (100 mg, 0.31 mmol) and furan-3-boronic acid (58 mg, 0.52 mmol) gave the title compound (18 mg). MS(ES+) m/e 323 $[M+H]^+$.

Example 10

Preparation of 4-[1-(5-aminopentyl)-4-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

a) *N*-(3-Nitro-4-pyridinyl)-1,5-pentanediamine

1,5-Pentanediamine (12.7 g, 125 mmol) was added to a suspension of 4-(methyloxy)-3-nitropyridine (3.85 g, 25 mmol) and Et_3N (4.13 mL, 30 mmol) in EtOH (25 mL) at RT. The reaction was then heated to reflux for 16 h. After cooling to RT, the reaction mixture was concentrated *in vacuo* giving the desired material as an oil that solidified on standing (6.20 g). This was used without any further purification. MS(ES) m/z 225 $[M+H]^+$.

b) 2-{5-[(3-Nitro-4-pyridinyl)amino]pentyl}-1*H*-isoindole-1,3(2*H*)-dione

Phthalic anhydride (6.2 g, 42 mmol) was added to the compound of Example 10(a) (6.2 g, 28 mmol) in acetic acid (70 mL). The reaction was heated to reflux for16 h and then allowed to cool to RT. The solvent was removed *in vacuo* to a residue suspended and vigorously stirred in aqueous $NaHCO_3$ for 1 h. The resulting solid was isolated by filtration and dried under vaccum. The filtrate was extracted EtOAc and the combined organic extracts dried over Na_2SO_4 and

combined with the previously isolated solid. The suspension was heated to reflux for 30 min and filtered hot. The filtrated was concentrated *in vacuo* and the resulting solid was dried under vaccum to give the desired material (7.65 g). This was used without any further purification. MS(ES) m/z 355 $[M+H]^+$.

c) 2-{5-[(3-Amino-2-chloro-4-pyridinyl)amino]pentyl}-1*H*-isoindole-1,3(2*H*)-dione

A suspension of Example 10(b) (7.65 g, .22 mmol) and conc. HCl (90 mL) was stirred at 90 °C for 10min. The heating bath was removed and tin (II) chloride (24 g, 108 mmol) was added portion wise over 2 min. The reaction was then heated at 90°C for an additional 30min. The reaction mixture was then concentrated *in vacuo* to 1/2 volume, cooled in an ice bath and adjusted to pH 10 with conc NH_4OH. The resulting precipitate was isolated by filtration and washed sequentially 1M NaOH and water and then dried under vacuum. The was suspended in EtOAC and heated to reflux for 30 min. The suspension was filtered hot and the filtrate was concentrated *in vacuo* to give the desired material as a solid (4.70 g). This was used without any further purification. MS(ES) m/z 359 $[M+H]^+$.

d) {4-Chloro-1-[5-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)pentyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}acetonitrile

Methyl cyanoacetate (11.5 mL, 13 mmol) was added to a solution of the compound of Example 10(c) (4.7 g, 13 mmol) in dimethylacetamide(12 mL). The resulting solution was heated to 166 °C for 2 h. The reaction was allowed to cool and then placed into an ice bath. MeOH (50 mL) was added and the solution was placed into a freezer overnight. The resulting precipitate was isolated by filtration and washed with cold MeOH. The filtrate was concentrated *in vacuo* and MeOH was added to the residue. The resulting solution was cooled in a freezer, and the resulting precipitate was isolated by filtration and washed with cold MeOH. The combined precipitates were dried under vacuum to give the desired compound (3.00 g). This was used without any further purification. MS(ES) m/z 408 $[M+H]^+$.

e) (2*E*)-{4-Chloro-1-[5-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)pentyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}(hydroxyimino)ethanenitrile

Sodium nitrite (1.02 g, 15 mmol)was added to a suspension of the compound of Example 10(d) (3.0 g, 7.4 mmol) in MeOH (60 mL) and 2N HCl (20 mL). After stirring for 16 h, the suspension was cooled in an ice bath and the solid isolated by filtration. The solid was washed with cold 50% water/MeOH and dried

under vaccum to give the desired compound (3 g,) which was used without further purification. MS(ES) m/z 437 $[M+H]^+$.

f) 2-{5-[2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-chloro-1*H*-imidazo[4,5-*c*]pyridin-1-yl]pentyl}-1*H*-isoindole-1,3(2*H*)-dione

Hydroxylamine (50wt. % in water, 1.1 mL, 17 mmol), the compound of Example 10(e) (3 g, 7.0 mmol), Et_3N (3.6 mL) and THF (60 mL) were combined in a pressure bottle. The reaction vessel was capped and heated to 90 °C for 1h. After cooling to RT, the reaction was diluted with EtOAc (250 mL) and washed with water (25 mL). The combined organic extracts were dried over $Na_2SO_4$and concentrated *in vacuo*. The resulting residue was dissolved in dioxane (40 mL) and Et_3N (3.0 mL) and heated to 140°C for 1h in a sealed pressure bottle. After cooling to RT, the reaction was diluted with EtOAc (250 mL), washed with water (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (silica gel, 5% to 20% EtOAc/CH_2Cl_2)gave the desired compound (1.26 g). MS(ES) m/z 452 $[M+H]^+$.

g) 2-{5-[2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-phenyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]pentyl}-1*H*-isoindole-1,3(2*H*)-dione

Dichlorobis(triphenylphosphine)palladium(II) (.019g, .027mmol) was added to a suspension of the compound of Example 10(f) (80 mg, 0.18 mmol) and benzeneboronic acid (43 mg, 0.35 mmol) in toluene (4 mL) and 2M Na_2CO_4 (0.4 mL) at 75 °C under nitrogen. After heating the reaction to 105 °C for 1 h, the solvent was removed *in vacuo*. Flash chromatography (silica gel, 8% EtOAc/CH_2Cl_2) gave the desired compound (70 mg). MS(ES) m/z 494 $[M+H]^+$.

h) 4-[1-(5-Aminopentyl)-4-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

Hydrazine hydrate (0.05 mL) was added to a suspension of the compound of Example 10(g) (47 mg, 0.09 mmol) in EtOH (1 mL). After heating to 78°C for 2 h, the solvent was removed *in vacuo*. Preparative HPLC (YMC Combiscreen ODS-A 50x20mm, 20 mL/min, gradient, A:CH_3CN-.1%TFA, B:water-.1% TFA, 10-50% A during 7min, UV detection at 214). gave the title compound (33 mg) as a TFA salt. MS(ES) m/z 364 $[M+H]^+$.

Example 11

Preparation of 4-[1-(6-aminohexyl)-4-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

a) 2-{6-[2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-chloro-1*H*-imidazo[4,5-*c*]pyridin-1-yl]hexyl}-1*H*-isoindole-1,3(2*H*)-dione

Following the procedures of Example 10(a) to Example 10(f), substituting 1,6-hexanediamine for 1,5-pentanediamine, gave the desired compound (2.68 g). MS(ES) m/z 466 $[M+H]^+$.

b) 2-{6-[2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-phenyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]hexyl}-1*H*-isoindole-1,3(2*H*)-dione

In a manner analogous to the preparation of the compound of Example 10(g), the compound of Example 11(a) (100 mg, 0.21 mmol) and benzeneboronic acid (52 mg, 0.43 mmol) gave the desired compound (100 mg). MS(ES) m/z 508 $[M+H]^+$.

c) 4-[1-(6-Aminohexyl)-4-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

In a manner analogous to the preparation of the compound of Example 10(h), the compound of Example 11(a) (55 mg, 0.11 mmol)gave the title compound (32 mg) as a TFA salt. MS(ES) m/z 378 $[M+H]^+$.

Example 12

Preparation of 4-[1-(5-aminopentyl)-4-(3-chlorophenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

a) 2-{5-[2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]pentyl}-1*H*-isoindole-1,3(2*H*)-dione

In a manner analogous to the preparation of the compound of Example 10(g), the compound of Example 10(f) (100 mg, 0.21 mmol) and 3-chlorophenylboronic acid (66 mg, 0.42 mmol) gave the desired compound (90 mg). MS(ES) m/z 528 $[M+H]^+$.

b) 4-[1-(5-Aminopentyl)-4-(3-chlorophenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

In a manner analogous to the preparation of the compound of Example 10(h), the compound of Example 12(a) (56 mg, 0.11 mmol)gave the title compound (40 mg) as a TFA salt. MS(ES) m/z 398 $[M+H]^+$.

Example 13

Preparation of 4-[1-(6-aminohexyl)-4-(3-chlorophenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

a) 2-{6-[2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]hexyl}-1*H*-isoindole-1,3(2*H*)-dione

In a manner analogous to the preparation of the compound of Example 10(g), the compound of Example 11(a) (100 mg, 0.21 mmol) and 3-chlorophenylboronic acid (66 mg, 0.42 mmol) gave the desired compound (100 mg). MS(ES) m/z 542 $[M+H]^+$.

b) 4-[1-(6-Aminohexyl)-4-(3-chlorophenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

In a manner analogous to the preparation of the compound of Example 10(h), the compound of Example 13(a) (56 mg, 0.10 mmol)gave the title compound (37 mg) as a TFA salt. MS(ES) m/z 412 $[M+H]^+$.

Example 14

Preparation of 4-[1-(3-amino-2,2-dimethylpropyl)-4-(3-methoxyphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

a) 4-[1-(3-Amino-2,2-dimethylpropyl)-4-chloro-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

A solution of the compound of Example 3(g) (0.385 g, 0.85 mmol) in a mixture of EtOH (15 mL) and hydrazine hydrate (0.4 mL) was heated at reflux for 2 h. The reaction mixture was cooled, filtered and the filtrate concentrated *in vacuo* to give 0.27 g of the desired compound. MS (ES) m/z 322.2 $[M+H]^+$.

b) 4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-methoxyphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

In a procedure similar to Example 3(h), 3-methoxyphenylboronic acid (0.046 g, 0.30 mmol) and the compound of Example 14(a) (0.075 g, 0.23 mmol) gave the title compound. MS (ES) m/z 394.2 $[M+H]^+$.

Example 15

Preparation of 4-[1-(5-aminopentyl)-4-(3-thienyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

a) 2-{5-[2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-(3-thienyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]pentyl}-1*H*-isoindole-1,3(2*H*)-dione

In a manner analogous to the preparation of the compound of Example 10(g), the compound of Example 10(f) (100 mg, 0.21 mmol) and thiophene-3-boronic acid (66 mg, 0.42 mmol) gave the desired compound (63 mg). MS(ES) m/z 500 $[M+H]^+$.

b) 4-[1-(5-Aminopentyl)-4-(3-thienyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

In a manner analogous to the preparation of the compound of Example 10(h), the compound of Example 15(a) (63 mg, 0.13 mmol)gave the title compound (40 mg) as a TFA salt. MS(ES) m/z 370 $[M+H]^+$.

Example 16

Preparation of 4-[1-(6-aminohexyl)-4-(3-thienyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

a) 2-{6-[2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-(3-thienyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]hexyl}-1*H*-isoindole-1,3(2*H*)-dione

In a manner analogous to the preparation of the compound of Example 10(g), the compound of Example 11(a) (100 mg, 0.21 mmol) and thiophene-3-boronic acid (55 mg, 0.42 mmol) gave the desired compound (98 mg). MS(ES) m/z 514 $[M+H]^+$.

b) 4-[1-(6-Aminohexyl)-4-(3-thienyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

In a manner analogous to the preparation of the compound of Example 10(h), the compound of Example 16(a) (56 mg, 0.10 mmol) gave the title compound (35 mg) as a TFA salt. MS(ES) m/z 384 $[M+H]^+$.

Example 17

4-[4-phenyl-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 18

4-[4-(3-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 19

4-[4-(4-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 20

4-[1-(3-aminopropyl)-4-(2-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 21

4-[1-(3-aminopropyl)-4-(1-piperidinyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 22

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-phenyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

Example 23

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-thiophen-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

Example 24

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

Example 25

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

Example 26

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-furan-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

Example 27

1-[2-(4-Amino-furazan-3-yl)-4-chloro-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

Example 28

1-[2-(4-Amino-furazan-3-yl)-4-(1H-pyrrol-2-yl))-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

Example 29

1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-methoxyphenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

Example 30

Preparation of 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone

a) 5-Bromo-2-chloro-N^4-ethyl-pyridine-3,4-diamine

To a solution of ethyl (3-bromo-5-nitropyridin-4-yl)amine (22.0 g, 89.4 mmol) in concentrated HCl (250 mL) was added in portions tin(II) chloride dihydrate (60.5 g, 270 mmol). The mixture was stirred 1 h at room temperature then poured into ice (300 g). EtOAc (500 mL) was added and the mixture made basic with NaOH. The layers were separated and the organic extract washed with water then brine, dried (Na_2SO_4) and all volatiles removed. The residue was purified by chromatography on silica eluted with 25% EtOAc, 75% hexanes to afford the title compound (17.8 g, 80%). MS: $(M+H)^+$ = m/z 250.

b) N-(5-Bromo-2-chloro-4-ethylamino-pyridin-3-yl)-cyanoacetamide

To a solution of 5-bromo-2-chloro-N^4-ethyl-pyridine-3,4-diamine (17.7 g, 70.9 mmol)in DMF (100 mL) stirred at 0 °C was added cyanoacetic acid (9.06 g, 106 mmol), N-methyl morpholine (39 mL, 350 mmol) and EDCI (20.3 g, 106 mmol). The cooling bath was removed and stirring continued 3h. EtOAc (300 mL) was added and the resulting mixture was washed with water then brine. crystallization from EtOAc / hexanes afforded the title compound (22.5 g, quantative). MS: $(M+H)^+$ = m/z 317.

c) (7-Bromo-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-acetonitrile

A solution of N-(5-bromo-2-chloro-4-ethylamino-pyridin-3-yl)-cyanoacetamide (35.6 g, 112 mmol) in acetic acid (300 mL) was stirred at 90 °C for 1h. All volatiles were removed to afford the title compound used as is in the next step (29.5 g). MS: $(M+H)^+$ = m/z 299.

d) (7-Bromo-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-hydroxyimino-acetonitrile

To a mixture of (7-bromo-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-acetonitrile (29.5 g, 98 mmol) in 2 N HCl (400 mL) was added portion wise, at room temperature, over 20 min sodium nitrite (14.0 g, 203 mmol). After stirring an additional 30 min the precipitated product was filtered, washed with water and dried

to afford the title compound used as is in the next step (32 g, quant.). MS: $(M+H)^+$ = m/z 328.

e) 4-(7-Bromo-4-chloro-1-ethyl-1H -imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine

A solution of (7-bromo-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-hydroxyimino-acetonitrile (98 mmol crude from previous step) in THF (250 mL) with TEA (40 mL) and 50% hydroxyl amine in water (16 mL) was stirred in a sealed flask at 90 °C for 1.5 h. The solution was cooled to room temperature then partitioned between EtOAc and water. The organic extract was washed with brine, dried and all volatiles removed. the residue was dissolved in dioxane (200 mL) with TEA (35 mL) and stirred in a sealed flask at 150 °C for 1.5 h. The solvent was removed *in vacuo* and the residue crystallized from methylene chloride to afford the title compound (17.3 g, 51% for three steps). MS: $(M+H)^+$ = m/z 343.

f) [4-(7-Bromo-4-chloro-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-yl]carbamic acid *tert*-butyl ester

The title compound was prepared from 4-(7-bromo-4-chloro-1-ethyl-1H -imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine using the procedure described in example 1-f (169 mg, 89%) MS: $(M+H)^+$ = m/z 443.

g) 2-(4-*tert*-Butoxycarbonylaminofurazan-3-yl)-4-chloro-1-ethyl-1*H* -Butoxycarbonylaminofurazan-3-yl)-4-chloro-1-ethyl-1*c*]pyridine-7-carboxylic acid

To a solution of [4-(7-bromo-4-chloro-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-yl]carbamic acid *tert*-butyl ester (1.0 g, 2.25 mmol) in dry THF stirred at –78 °C under N_2 was added *n*-butyl lithium (2.7 mL of 2.5 M solution in hexanes, 6.75 mmol) rapidly dropwise. This was stirred 1 min then CO_2 was bubbled through the solution for 30 min while the temperature was maintained at –78 °C. The mixture was allowed to warm to room temperature then partitioned between EtOAc and 1 N HCl. The organic extract was washed with water then brine and dried (Na_2SO_4). The organic solution was passed through a silica plug then all volatiles were removed *in vacuo* to afford the title compound (620 mg, 67%). MS: $(M+H)^+$ = m/z 409.

h) (4-{7-[1-(3-*tert* -Butoxycarbonylaminopyrrolidin-1-yl)methanoyl]-4-chloro-1-ethyl-1*H* -imidazo[4,5-*a*]pyridin-2-yl}furazan-3-yl)carbamic acid *tert*-butyl ester

A mixture consisting of 2-(4-*tert*-Butoxycarbonylaminofurazan-3-yl)-4-chloro-1-ethyl-1*H* -Butoxycarbonylaminofurazan-3-yl)-4-chloro-1-ethyl-1*c*]pyridine-7-

carboxylic acid (410 mg, 1 mmol), Pyrrolidin-3-yl-carbamic acid *tert* -butyl ester (327 mg, 2 mmol), HOAT (272 mg, 2 mmol), EDCI (383 mg, 2 mmol) and N-methyl morpholine (2 mL) in DMF (4 mL) was stirred at room temperature for 20 h. The mixture was partitioned between EtOAc and 1 N HCl. The organic extract was washed with water then brine, dried (Na_2SO_4) and all volitiles removed *in vacuo*. Chromatography on silica (eluted with75% EtOAc, 25% hexanes) afforded the title compound (375 mg, 81%). MS: $(M+H)^+$ = m/z 577.

i) {4-[7-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-ylmethyl)-4-(3-chlorophenyl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-yl}carbamic acid *tert*-butyl ester

A mixture consisting of (4-{7-[1-(3-*tert* -Butoxycarbonylaminopyrrolidin-1-yl)methanoyl]-4-chloro-1-ethyl-1*H* -imidazo[4,5-*a*]pyridin-2-yl}furazan-3-yl)carbamic acid *tert*-butyl ester (100 mg, 0.17 mmol), 3-chlorophenylboronic acid (53 mg, 0.34 mmol) and tetrakis(triphenylphosphine)palladium(0) (25 mg) in toluene (2.3 mL) with EtOH (0.25 mL) and 2 M aqueous Na_2CO_3 solution (0.30 mL) was stirred at 90 °C for 18 h in a sealed tube. The organic solution was separated and chromatographed on silica (eluted with 60% EtOAc, 40% hexanes) to afford the title compound (130 mg, 86%). MS: $(M+H)^+$ = m/z 653.

j) 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chlorophenyl)-1*H*-imidazo[4,5-*c*]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone

A solution of {4-[7-((S)-3-*tert*-butoxycarbonylaminopyrrolidin-1-ylmethyl)-4-(3-chlorophenyl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-yl}carbamic acid *tert*-butyl ester (130 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) with TFA (1 mL) was sstirred at room temperature for 1h. All volatiles were removed and the residue purified by HPLC (acetonitrile water gradient 0.1% TFA) to afford the title compound (61 mg, 68%). MS: $(M+H)^+$ = m/z 453.

Examples 22-29, 31-46, 48, 49, 51-53, 55-58, 60, 62 and 66-70

These compounds were prepared in a manner analogous to the preparation of the compound of Example 30.

Example	Name	$[M+H]^+$
22	1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-phenyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone	419
23	1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-thiophen-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone	425
24	1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone	420
25	1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone	420
26	1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-furan-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone	409
27	1-[2-(4-Amino-furazan-3-yl)-4-chloro-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone	409
28	1-[2-(4-Amino-furazan-3-yl)-4-(1H-pyrrol-2-yl))-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone	408
29	1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-methoxyphenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone	449
31	1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-furan-2-yl-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone	409
32	2-(4-Amino-furazan-3-yl)-1-ethyl-4-phenyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide	518
33	2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide	552
34	2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2,3-dichloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide	588
35	2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-chloro-phenyl)-1H-	552

	imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide	
36	2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-hydroxy-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide	534
37	2-(4-Amino-furazan-3-yl)-4-(3-chloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide	453
38	2-(4-Amino-furazan-3-yl)-4-phenyl-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide	419
39	2-(4-Amino-furazan-3-yl)-4-(5-chloro-thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide	459
40	2-(4-Amino-furazan-3-yl)-4-(2-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide	434
41	2-(4-Amino-furazan-3-yl)-4-(3-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide	434
42	2-(4-Amino-furazan-3-yl)-4-(3-bromo-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide	497
43	2-(4-Amino-furazan-3-yl)-4-(1-naphthalenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide	469
44	2-(4-Amino-furazan-3-yl)-4-(thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide	425
45	2-(4-Amino-furazan-3-yl)-4-(3,4-methylenedioxyphenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide	463
46	2-(4-Amino-furazan-3-yl)-4-(3,5-dichloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide	487
48	4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-biphenylyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine	495
49	4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,4-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine	407
51	2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol	435
52	4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2-chlorophenyl)-1-	453

	ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine	
53	(2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenyl)methanol	449
55	4-(1-ethyl-7-{[3-(methylamino)-1-pyrrolidinyl]carbonyl}-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine	433
56	4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(4-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine	433
57	4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,5-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine	487
58	4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(1-benzothien-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine	475
60	4-{7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-[4-(methyloxy)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-1,2,5-oxadiazol-3-amine	449
62	4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine	453
66	3-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol	435
67	4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}benzonitrile	444
68	1-[2-(4-Amino-furazan-3-yl)-4-phenyl-1-piperidin-4yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone	474
69	4-(4-(3-chlorophenyl)-1-ethyl-7-{[3-(methylamino)-1-pyrrolidinyl]carbonyl}-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine	467
70	4-(4-(2,5-dichlorophenyl)-1-ethyl-7-{[3-(methylamino)-1-pyrrolidinyl]carbonyl}-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine	501

Example 31

1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-furan-2-yl-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

Example 32

2-(4-Amino-furazan-3-yl)-1-ethyl-4-phenyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

Example 33

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

Example 34

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2,3-dichloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

Example 35

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

Example 36

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-hydroxy-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

Example 37

2-(4-Amino-furazan-3-yl)-4-(3-chloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

Example 38

2-(4-Amino-furazan-3-yl)-4-phenyl-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

Example 39

2-(4-Amino-furazan-3-yl)-4-(5-chloro-thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

Example 40

2-(4-Amino-furazan-3-yl)-4-(2-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

Example 41

2-(4-Amino-furazan-3-yl)-4-(3-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

Example 42

2-(4-Amino-furazan-3-yl)-4-(3-bromo-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

Example 43

2-(4-Amino-furazan-3-yl)-4-(1-naphthalenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

Example 44

2-(4-Amino-furazan-3-yl)-4-(thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

Example 45

2-(4-Amino-furazan-3-yl)-4-(3,4-methylenedioxyphenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

Example 46

2-(4-Amino-furazan-3-yl)-4-(3,5-dichloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

Example 47

Preparation of 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine, trifluoroacetate salt

a) Cyclopropylmethyl-(3-nitropyridin-4-yl)amine

4-Ethoxy-3-nitropyridine, hydrochloride (14.5 g, 70.8 mmol) in ethyl acetate was washed twice with 1N $NaHCO_3$. The organic layer was dried over MgSO4, filtered and the solvent evaporated under reduced pressure to give 11.8 g of a light tan solid. The free-amine (11.8 g, 69.9 mmol) and cyclopropanemethylamine (5.00 g, 70.3 mmol) in EtOH were heated at 80 °C in a sealed tube for 12 h. After allowing to warm to RT, the solvent was removed under reduced pressure to give a yellow oil. Flash chromatography (silica gel, hexanes then hexanes/Et_2O (1:1:1) then Et_2O/CH_2Cl_2 (1:1) then CH_2Cl_2) gave 13.1 g of the desired material. MS (ES) m/z 194.2 $[M+H]^+$.

b) (3-Bromo-5-nitropyridin-4-yl)cyclopropylmethylamine

To the compound of Example 47(a) (13.1 g, 68.0 mmol) and NaOAc (25.1 g, 305.5 mmol) in glacial acetic acid (20 mL) was added bromine (15.6 g, 97.6 mmol). The reaction was maintained at 100 °C for 20 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 and filtered. The solvent was removed from the filtrate under reduced pressure and the residue purified by flash chromatography (silica gel, 0% to 20% EtOAc/hexanes) to give 9.81 g of the desired product as a yellow oil. MS (ES) m/z 272.2 $[M+H]^+$.

c) 5-Bromo-2-chloro-N^4-cyclopropylmethylpyridine-3,4-diamine

The compound of Example 47(b) (3.11 g, 11.43 mmol) was dissolved into ethanol (25 mL) and cooled to 0 °C. Concentrated HCl (25 mL) was added while maintaining the reaction at 0 °C. After 15 min., tin (II) chloride (6.55 g, 34.5 mmol) was added. After 3 h at 0 °C, the reaction mixture was poured into a solution of NaOH (24 g, 600 mmol) in ice water (75 mL). The mixture was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure to give 3.05 g of the desired material. This was used without further purification. MS (ES) m/z 276.0 $[M+H]^+$.

d) [7-Bromo-4-chloro-1-(cyclopropylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]acetonitrile

The compound of Example 47(c) (2.60 g, 9.40 mmol) in ethyl cyanoacetate (10.6 g, 93.8 mmol) was heated to 190 °C for 3 h. The reaction was allowed to cool to RT. Flash chromatography (silica gel, 50% $Et_2O/CHCl_3$) gave 1.62 g of the desired material. MS(ES) m/z 325.0 $[M+H]^+$.

e) (7-Bromo-4-chloro-1-cyclopropylmethyl-1H-imidazo[4,5-c]pyridin-2-yl)hydroxyimino-acetonitrile

To the compound of Example 47(d) (1.32 g, 4.65 mmol) in MeOH (30 mL) and 2N HCl (15 mL) was added sodium nitrite (0.59 g, 8.55 mmol). After stirring at RT for 1 h, the precipitate was collected by filtration and dried under vacuum to give 1.35 g of the desired material as a yellow powder. This was used without further purification. MS (ES) m/z 354.0 $[M+H]^+$.

f) 2-(7-Bromo-4-chloro-1-cyclopropylmethyl-1H-imidazo[4,5-c]pyridin-2-yl)-N-hydroxy-2-hydroxyimino acetamidine

To the compound of Example 47(e) (1.35 g, 3.80 mmol) and Et_3N (1.46 g, 14.4 mmol) in THF (20 mL) was added hydroxylamine (0.70 mL, 10.6 mmol). The reaction was heated at 90 °C for 1 h. After allowing to cool to RT, the reaction was diluted with EtOAc and washed with H_2O and brine. The organic extract was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 1.56 g of the desired material as a yellow oil. This was used without further purification. MS (ES) m/z 387.0 $[M+H]^+$.

g) 4-(7-Bromo-4-chloro-1-cyclopropylmethyl—1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine

The compound of Example 47(f) (1.57 g, 3.80 mmol) and Et3N (2.18 g, 21.5 mmol) in 1,4-dioxane was heated at 150 °C in a sealed tube for 1 h. After allowing to cool to RT, the crude reaction mixture purified by flash chromatography (silica gel, 0% to 20 % EtOAc/hexanes) to give 0.90 g of the desired product as a cream colored solid. MS (ES) m/z 368.8 $[M+H]^+$.

h) [4-(7-Bromo-4-chloro-1-cyclopropylmethyl-*1H*-imidazo[4,5-c]pyridin-2-yl)furazan-3-yl]di-*tert*-butoxycarbonylamine

To the compound of Example 47(g) (0.90 g, 2.43 mmol) in $CHCl_3$ (20 mL) was added di-*tert*-butyldicarbonate (1.12 g, 5.14 mmol) and dimethylaminopyridine (67.7 mg, 0.55 mmol). The reaction was heated to reflux for 1 h. After allowing to cool to RT, the solvent was removed under reduced pressure. Trituration from hot MeOH gave 1.06 g of the desired material as a white powder. MS (ES) m/z 569.2 $[M+H]^+$.

i) 4-Chloro-1-(cyclopropylmethyl)-2-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1,2,5-oxadiazol-3-yl]-1*H*-imidazo[4,5-*c*]pyridine-7-carboxylic acid

A solution of the compound of Example 47(h) (0.84 g, 1.48 mmol) in dry THF (25 mL) was degased and then cooled to -78 °C. *n*-Butyllithium (1.50 mL of a 2.50 M solution in hexanes, 3.75 mmol) was added to the cooled solution. After 5 minutes, CO_2 gas was bubbled into the reaction for 1 h while continuing to maintain the reaction at -78 °C. The reaction was allowed to reach ambient temperature and diluted with EtOAc. The organic layer was washed with 1N NaOH and dried over $MgSO_4$. The solvent was removed under reduced pressure. Purification by preparative reverse phase HPLC (Phenomenex® Synergi MaxRP 80A column, gradient 10% AcCN/H_2O to 80% AcCN/H_2O + 0.1% TFA) gave 0.14 g of the desired material as a grey solid. MS(ES) m/z 435.4 $[M+H]^+$.

j) 1,1-Dimethylethyl [1-({4-chloro-1-(cyclopropylmethyl)-2-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1,2,5-oxadiazol-3-yl]-1*H*-imidazo[4,5-*c*]pyridin-7-yl}carbonyl)-3-pyrrolidinyl]carbamate

A solution of 3-(*tert*-butoxycarbonylamino)pyrrolidine (72.5 mg, 0.39 mmol) in CH_2Cl_2 was added to a solution of the compound of Example 47(i) (0.11 g, 0.24 mmol) in CH_2Cl_2. 1-Hydroxy-7-azabenzotriazole (49.3 mg, 0.36 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (84.1 mg, 0.44 mol) and Et_3N (145 mg, 1.44 mmol) were added sequentially. After 3 d at RT, the solvent was removed under reduced pressure. Flash chromatography (silica gel, 3%

EtOH/CHCl3) gave the desired product. This was further purified by crystalization from Et_2O/hexanes to give 0.11 g of the desired compound as a white solid. MS(ES) m/z 603.2 $[M+H]^+$.

k) 4-[7-[(3-Amino-1-pyrrolidinyl)carbonyl]-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine, trifluoroacetate salt

To a degased mixture of the compound of Exampel 47(j) (39.2 mg, 0.06 mmol), 3-chlorophenylboronic acid (22.8 mg, 0.14 mmol) and 2.0M Na_2CO_3 (0.20 mL, 0.40 mmol) in EtOH/toluene (1:1 v/v, 10 mL) was added $(Ph_3P)_4Pd$ (13.5 mg). After 4 hours at 125 °C, the reaction was allowed to cool to room temperature, diluted with MeOH and filtered. The filtrate evaporated under reduced pressure and the resulting residue was dissolved in 4N HCl/dioxane. After 3.5 h the solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (5 mL) and trifluoroacetic acid (5 mL). After 1 h, the solvent was removed under reduced pressure and the residue subjected to preparative reverse phase HPLC (Phenomenex® Synergi MaxRP 80A column, gradient 10% AcCN/H_2O to 80% AcCN/H_2O + 0.1% TFA) to give 15.2 mg of the title compound as a white powder. MS (ES) m/z 479.2 $[M+H]^+$.

Example 48

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-biphenylyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 49

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,4-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 50

Preparation of 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(phenylethynyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

a) (4-{7-[1-(3-tert-Butoxycarbonylamino-pyrrolidin-1-yl)-methanoyl]-1-ethyl-4-phenylethynyl-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-yl)-carbamic acid *tert*-butyl ester

A mixture consisting of (4-{7-[1-(3-*tert* -butoxycarbonylaminopyrrolidin-1-yl)methanoyl]-4-chloro-1-ethyl-1*H* -imidazo[4,5-*a*]pyridin-2-yl}furazan-3-yl)carbamic acid *tert*-butyl ester (100 mg, 0.17 mmol), ethynylbenzene (42 mg, 0.41 mmol) and bis(benzonitrile)palladium(II) chloride (12 mg, 0.03 mmol), copper(I) iodide (3.9 mg, 0.02 mmol), tri-*tert*-butylphosphine and diisopropyl amine (0.17 mL, 0.85 mmol) in dioxane (2 mL) was stirred at 80 °C for 18 h in a sealed tube. Additional ethynylbenzene (42 mg, 41 mmol) was added and stirring at 80 °C continued for 4h. Removal of all volatiles followed by chromatography on silica (eluted with 70% EtOAc, 30% hexanes) afforded the title compound (60 mg, 55%). MS: $(M+H)^+$ = m/z 643.

b) 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-phenylethynyl-1H-imidazo[4,5-]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone

The title compound was prepared from (4-{7-[1-(3-tert-Butoxycarbonylamino-pyrrolidin-1-yl)-methanoyl]-1-ethyl-4-phenylethynyl-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-yl)-carbamic acid *tert*-butyl ester using the method described in example 30(j) (27 mg, 66%). MS: $(M+H)^+$ = m/z 443.

Example 51

2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;

Example 52

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 53

(2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenyl)methanol;

Example 54

Preparation of 2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}-4-chlorophenol

The title compound was prepared in an analogous fashion to the preparation of the compound of Example 61. MS: $(M+H)^+$ = m/z 469.

Example 55

4-(1-ethyl-7-{[3-(methylamino)-1-pyrrolidinyl]carbonyl}-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;

Example 56

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(4-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 57

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,5-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 58

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(1-benzothien-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 59

Preparation of 4-[1-ethyl-4-phenyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

a) 4-[2-(4-tert-Butoxycarbonylamino-furazan-3-yl)-4-chloro-1-ethyl-1H -imidazo[4,5-c]pyridin-7-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester

The title compound was prepared from [4-(7-bromo-4-chloro-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-yl]carbamic acid *tert*-butyl ester using the methods described in example 65(g) and 65(h) (295 mg, 28%). MS: $(M+H)^+$ = m/z 564.

b) 4-[1-Ethyl-4-phenyl-7-(piperidin-4-yloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

The title compound was prepared from 4-[2-(4-tert-butoxycarbonylamino-furazan-3-yl)-4-chloro-1-ethyl-1H -imidazo[4,5-c]pyridin-7-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester using the methods described in example 30(i) and 30(j) (67 mg, 76%). MS: $(M+H)^+$ = m/z 406.

Example 60

4-{7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-[4-(methyloxy)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-1,2,5-oxadiazol-3-amine;

Example 61

Preparation of 4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol

To a stirred solution of {4-[7-[1-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-methanoyl]-1-ethyl-4-(4-methoxyphenyl)-1*H* -imidazo[4,5-*c*]pyridin-2-yl]furazan-3-yl}-carbamic acid *tert*-butyl ester (140 mg, 0.21 mmol) (prepared by the methods described in example 30(i)) in methylene chloride (10 mL) at -78 ^oC was added dropwise boron tribromide (2.1 mL of 1 M soln in methylene chloride, 2.1 mmol). The product mixture was evaporated three times from methanol. Purification by HPLC (acetonitrile water gradient with 0.1%TFA) afforded the title compound (51 mg, 56%). MS: $(M+H)^+$ = m/z 435.

Example 62

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 63

Preparation of 4-[4-(3-chlorophenyl)-1-ethyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

The title compound was prepared in an analogous fashion to the preparation of the compound of Example 59. MS: $(M+H)^+$ = m/z 440.

Example 64

Preparation of 2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-*N*-{2-[(phenylmethyl)amino]ethyl}-1*H*-imidazo[4,5-*c*]pyridine-7-carboxamide, trifluoroacetate salt

a) 4-(3-Chlorophenyl)-1-(cyclopropylmethyl)-2-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1,2,5-oxadiazol-3-yl]-1*H*-imidazo[4,5-*c*]pyridine-7-carboxylic acid

To a solution of the compound of Example 47(i) (100 mg, 0.23 mmol) and 3-chlorophenylboronic acid (47.5 mg, 0.30 mmol) in EtOH (10 mL) and toluene (10 mL) was added 2M Na_2CO_3 (0.70 mL, 1.40 mmol). The mixture was degased and $(Ph_3P)_4Pd$ (48.1 mg.; 0.04 mmol) was added. The reaction was heated to reflux for 6 h. After allowing to cool to RT, the reaction mixture was filtered and the filtrate was concentrated. Flash chromatography (silica gel, 10% to 25% EtOH/CHCl3) gave 135 mg of the desired material as a white solid. MS (ES) m/z 511.4 $[M+H]^+$.

b) 1,1-Dimethylethyl (4-{4-(3-chlorophenyl)-1-(cyclopropylmethyl)-7-[({2-[(phenylmethyl)amino]ethyl}amino)carbonyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}-1,2,5-oxadiazol-3-yl)carbamate

To the compound of Example 64(a) (37.2 mg, 0.073 mmol) in CH_2Cl_2 and DMF was added N-benzylethylenediamine (20 mg, 0.13 mmol), 1-hydroxy-7-azabenzotriazle (17.5 mg, 0.13 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (27.8 mg, 0.15 mmol) and triethylamine (43.7 mg, 0.43 mmol). After 6 d at RT, the solvent was removed under reduced pressure. Flash chromatography (silica gel, 5% MeOH/$CHCl_3$) gave 27.4 mg of the desired material as a tan oil. MS (ES) m/z 643.4 $[M+H]^+$.

c) 2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-*N*-{2-[(phenylmethyl)amino]ethyl}-1*H*-imidazo[4,5-*c*]pyridine-7-carboxamide, trifluoroacetate salt

The compound of Example 64(b) (27.4 mg) was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (10 mL). After 1 h at RT, the solvent was removed

under reduced pressure. Trituration with Et_2O gave 13.8 mg of the title compound as a white powder. MS (ES) m/z 543.4 $[M+H]^+$.

Example 65

Preparation of 4-[1-Ethyl-7-(piperidin-4-yloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

a) Ethyl (3-nitropyridin-4-yl)amine

A solution consisting of 4-methoxy-3-nitropyridine (15.0 g, 97.3 mmol)with ethyl amine (46.5 mL of 70% aqueous solution, 584 mmol) in ethanol (30 mL) was stirred at 85 °C in a sealed flask for 2 h. Removal of all volatiles *in vacuo* afforded the title compound (16.2 g, 99 %). MS: $(M+H)^+$ = m/z 168.

b) Ethyl (3-bromo-5-nitropyridin-4-yl)amine

A mixture consisting of ethyl (3-nitropyridin-4-yl)amine (11.76 g, 70 mmol) in acetic acid (140 ml) with sodium acetate (28.7 g, 350 mmol) and bromine (13.44 g, 84 mmol) was stirred in a sealed flask at 100 °C for 18 h. Most of the solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 and water and the aqueous layer basified with $NaHCO_3$. The organic extract was washed with water then brine, dried (Na_2SO_4) and all volatiles removed *in vacuo*. The residue was chromatographed on silica gel eluted with ethyl acetate: hexane (2:8) to afford the title compound (10.4 g, 60%). MS: $(M+H)^+$ = m/z 246.

c) 5-Bromo-N^4-ethyl-pyridine-3,4-diamine

A mixture of ethyl (3-bromo-5-nitropyridin-4-yl)amine (7.0 g, 28.4 mmol) in acetic acid (100 mL) with iron powder (<50 micron, 9.51 g, 170 mmol) was stirred at 75 °C for 1 h. The reaction mixture was cooled then diluted with EtOAc:CH_2Cl_2 (1:4) and filtered through celite. The filtrate was concentrated *in vacuo* then chromatographed on silica gel eluted with ethyl acetate: methanol (96:4) to afford the title compound (5.68 g, 92.7%). MS: $(M+H)^+$ = m/z 216.

d) (7-Bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-acetonitrile

A solution of 5-Bromo-N^4-ethyl-pyridine-3,4-diamine (5.68 g, 26.3 mmol) in ethyl cyanoacetate (5.6 mL, 52.6 mmol) was stirred at 190 °C for 1 h. The product crystallized on cooling and addition of EtOAc (50 mL). The solid was collected,

washed with EtOAc then dried to afford the title compound (4.15 g, 59%). MS: $(M+H)^+$ = m/z 265.

e) 4-(7-Bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-[1,2,5]oxadiazolidin-3-ylamine

To a solution of (7-bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-acetonitrile (3.2 g, 12.1 mmol) in methanol (40 mL) was added in portions sodium nitrite (1.67 g, 24.2 mmol). The resulting mixture was stirred 2 h then adjusted to pH 12 with 50% aqueous NaOH. To this was added 50% aqueous NH_2OH (33 ml) and the mixture was stirred at 90 °C for 2 h. The solid which formed on cooling was collected by filtration to afford the title compound (2.50 g, 67%). MS: $(M+H)^+$ = m/z 309.

f) [4-(7-Bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-yl]-carbamic acid tert-butyl ester

A solution consisting of 4-(7-bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-[1,2,5]oxadiazolidin-3-ylamine (2.14 g, 6.95 mmol) in methylene chloride (10 mL) and pyridine (20 mL) with di-*t*-butyl dicarbonate (2.27 g, 10.43 mmol) and DMAP (0.85 g, 6.95 mmol) was stirred at 90 °C in a sealed tube for 2.5 h. Additional di-*t*-butyl dicarbonate (2.27 g, 10.43 mmol) was added and stirring at 90 °C continued for 18 h. The product mixture was partitioned between EtOAc and water, the layers separated and the organic extract washed with water then brine, dried (Na_2SO_4) and all volitiles removed *in vacuo*. The residue was chromatographed on silica 20% EtOAc in hexane to afford the title compound as an off-white solid 1.60 g, 58.4%) MS: $(M+H)^+$ = m/z 409.

g) [4-(1-Ethyl-7- hydroxy-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-yl]-carbamic acid tert-butyl ester

To a solution of [4-(7-bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-yl]-carbamic acid tert-butyl ester (205 mg, 0.5 mmol) in THF (4 mL) stirred at –78 °C under N_2 was added *n*-BuLi (0.5 ml of 2.5 M solution in hexane, 1.25 mmol). This was stirred at –78 °C for 20 min then trimethyl borate (168 uL, 1.5 mmol) with THF (1 mL) was added. Stirring was continued for 1.5 h while the reaction mixture was allowed to warm to room temperature. To the resulting mixture was added a solution consisting of 30% H_2O_2 (1.1 mL) in 3N NaOH (0.35 mL) and stirring continued at room temperature for 30 min. The reaction mixture was diluted with EtOAc then washed with 1N NaOH (3X). The combined aqueous extract was acidified with 6N HCl and the product extracted into EtOAc. The organic extract

was dried (Na_2SO_4) and all volitiles removed *in vacuo* to afford the product as an orange solid (144 mg, 83%). MS: $(M+H)^+$ = m/z 347.

h) 4-[2-(4-tert-Butoxycarbonylamino-furazan-3-yl)-1-ethyl-1H -imidazo[4,5-c]pyridin-7-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester

To a stirred mixture of triphenyl phosphine polystyrene (2.4 g, 1.2 mmol/g, 2.88 mmol) in CH_2Cl_2 (25 mL) was added 4-hydroxypiperidine-1-carboxylic acid *tert*-butyl ester (1.15 g, 5.76 mmol) followed by diethyl azodicarboxylate (0.45 mL, 2.88 mmol). After 10 min at room temperature the mixture was cooled to 0 °C and a solution of [4-(1-ethyl-7- hydroxy-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-yl]-carbamic acid tert-butyl ester (200 mg, 0.58 mmol) in CH_2Cl_2 (15 mL) was added. This was stirred 1.5 h at 0 °C then filtered. the resin was washed with CH_2Cl_2 and the combined organic extract washed with 1 N NaOH soln then water, dried (Na_2SO_4) and all volitiles removed. The residue was purified by preparative HPLC (eluted with CH_3CN / H_2O /0.1% TFA) to afford the title compound as an off white solid (131 mg, 43%). MS: $(M+H)^+$ = m/z 530.

i) 4-[1-Ethyl-7-(piperidin-4-yloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

A solution of 4-[2-(4-tert-butoxycarbonylamino-furazan-3-yl)-1-ethyl-1H - imidazo[4,5-c]pyridin-7-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester (130 mg, 0.25 mmol) in CH_2Cl_2 (1.5 mL) with TFA (0.75 mL) was stirred at room temperature for 40 min. Removal of all volatiles followed by purification by preparative HPLC (eluted with CH_3CN / H_2O) afforded the title compound (80 mg, 97%). MS: $(M+H)^+$ = m/z 330.

Example 66

3-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;

Example 67

4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}benzonitrile;

Example 68

1-[2-(4-Amino-furazan-3-yl)-4-phenyl-1-piperidin-4yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

Example 69

4-(4-(3-chlorophenyl)-1-ethyl-7-{[3-(methylamino)-1-pyrrolidinyl]carbonyl}-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;

Example 70

4-(4-(2,5-dichlorophenyl)-1-ethyl-7-{[3-(methylamino)-1-pyrrolidinyl]carbonyl}-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;

Example 71

Preparation of 4-[4-(2,5-dichlorophenyl)-1-ethyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine

The title compound was prepared in an analogous fashion to the preparation of the compound of Example 59. MS: $(M+H)^+$ = m/z 479.

Example 72

Preparation of 2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl-N-[3-(dimethylaminopropyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide, trifluoroacetate salt

a) 1,1-Dimethylethyl {4-[4-(3-chlorophenyl)-1-(cyclopropylmethyl)-7-({[3-(dimethylamino)propyl]amino}carbonyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-yl}carbamate

To the compound of Example 64(a) (41.2 mg, 0.081 mmol) and 3-dimethylaminopropylamine (16.2 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) and DMF (2 mL) was added 1-hydroxy-7-azabenzotriazole (17.0 mg, 0.12 mmol), 1-(3-

dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (28.6 mg, 0.15 mol) and Et_3N (43.7 mg, 0.43 mmol). After 6 d at RT, the solvent was removed under reduced pressure. Preparative reverse phase HPLC (Phenomenex® Synergi MaxRP 80A column, gradient 10% AcCN/H_2O to 80% AcCN/H_2O + 0.1% TFA) gave 37.5 mg of the desired material as a clear oil. MS (ES) m/z 595.4 $[M+H]^+$.

b) 2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cylopropylmethyl-N-[3-(dimethylaminopropyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide, trifluoroacetate

In a manner analogous to the preparation of the compound of Example 64(c), the compound of Example 72(a) (37.5 mg, 0.063 mmol) gave 12.6 mg of the title compound as a white powder following trituration from hexanes. MS (ES) m/z 496.4 $[M+H]^+$.

Example 73- Capsule Composition

An oral dosage form for administering the present invention is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table I, below.

Table I

INGREDIENTS	AMOUNTS
4-(4-Phenyl-1-piperidin-4-yl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

Example 74 - Injectable Parenteral Composition

An injectable form for administering the present invention is produced by stirring 1.5% by weight of 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-phenyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone in 10% by volume propylene glycol in water.

Example 75 - Tablet Composition

The sucrose, calcium sulfate dihydrate and an Akt inhibitor as shown in Table II below, are mixed and granulated in the proportions shown with a 10%

gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid;, screened and compressed into a tablet.

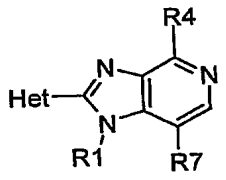
Table II

INGREDIENTS	AMOUNTS
2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-[3-(dimethylamino)propyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide	20 mg
calcium sulfate dihydrate	30 mg
sucrose	4 mg
starch	2 mg
talc	1 mg
stearic acid	0.5 mg

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

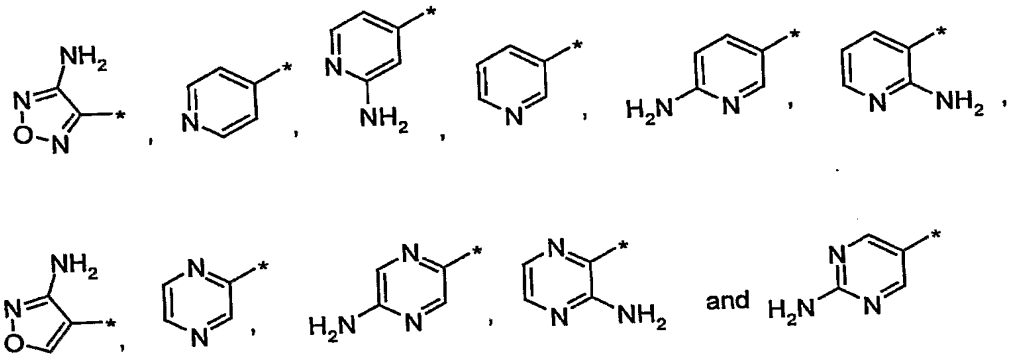
1. A compound of Formula (I):



(I)

wherein:

Het is selected from the group consisting of:



R^1 is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, $-C(O)OR^2$, $-C(O)NR^5R^6$, $-S(O)_2NR^5R^6$, $-S(O)_nR^2$ and protected -OH,

where n is 0-2,

R^2 is hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and

R^5 and R^6 are independently hydrogen, cycloalkyl, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH, or R^5 and R^6 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2; and

R^7 is selected from hydrogen, $-C(O)NR^9R^{10}$, $-(CH_2)_nNR^9R^{10}$, $-SO_2NR^9R^{10}$ and $-(CH_2)_nOR^8$,

where n is 0-2;

R^8 is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$,

-C(O)NR^2R^3, -$S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2,

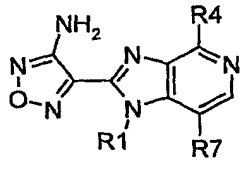
R^9 and R^{10} are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, -C(O)OR^2, -$S(O)_nR^2$, -$C(O)NR^2R^3$, -$S(O)_2NR^2R^3$, -NR^2R^3, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH,

or R^9 and R^{10} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2.

2. A pharmaceutically acceptable salt, hydrate, solvate or ester of a compound of Formula (I), as described in claim 1.

3. A compound of Claim 1 represented by the following Formula (II):



(II)

wherein:

R^1 is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, $-C(O)OR^2$, $-C(O)NR^5R^6$, $-S(O)_2NR^5R^6$, $-S(O)_nR^2$ and protected -OH, where n is 0-2,

R^2 is hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and

R^5 and R^6 are independently hydrogen, cycloalkyl, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH, or R^5 and R^6 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2; and

R^7 is selected from hydrogen, $-C(O)NR^9R^{10}$, $-(CH_2)_nNR^9R^{10}$, $-SO_2NR^9R^{10}$ and $-(CH_2)_nOR^8$,
where n is 0-2;
R^8 is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH,
where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2,
R^9 and R^{10} are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, $-NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected –OH,
or R^9 and R^{10} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,
where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2.

4. A pharmaceutically acceptable salt, hydrate, solvate or ester of a compound of Formula (II), as described in claim 3.

ABSTRACT OF THE DISCLOSURE

Invented are novel 1H-imidazo[4,5-c]pyridin-2-yl compounds, the use of such compounds as inhibitors of PKB/AKT kinase activity and in the treatment of cancer and arthritis.